3

ASD Symptoms in ADHD, an Independent Familial Trait?

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Abstract

The aims of this study were to investigate whether subtle Autism Spectrum Disorders (ASD) symptoms in the context of ADHD are transmitted in families independent of ADHD, and whether ASD symptom familiality is influenced by gender and age. The sample consisted of 256 sibling pairs with at least one child with ADHD and 147 healthy controls, aged 5-19 years. Children who fulfilled criteria for autistic disorder were excluded. The Children's Social Behavior Questionnaire (CSBQ) was used to assess ASD symptoms. Probands, siblings, and controls were compared using analyses of variance. Sibling correlations were calculated for CSBQ scores after controlling for IQ, ADHD, and comorbid anxiety. In addition, we calculated cross-sibling cross-trait correlations. Both children with ADHD and their siblings had higher ASD levels than healthy controls. The sibling correlation was 0.28 for the CSBQ total scale, with the CSBQ stereotyped behavior subscale showing the strongest sibling correlation (r=0.35). Sibling correlations remained similar in strength after controlling for IQ and ADHD, and were not confounded by comorbid anxiety. Sibling correlations were higher in female than in male probands. The social subscale showed stronger sibling correlations in elder than in younger sibling pairs. Cross-sibling cross-trait correlations for ASD and ADHD were weak and not-significant. The results confirm that children with ADHD have high levels of ASD symptoms, and further suggest that the familiality of subtle ASD symptoms in the context of ADHD is largely independent from ADHD familiality.

Introduction

Apart from the defining symptoms of inattention, hyperactivity, and/or impulsivity, many children with attention- deficit/hyperactivity disorder (ADHD) show problems in social functioning. Although children with ADHD generally do not lack interest in other people, they often fail to properly attune their behavior to other persons and to constantly changing social environments. The key characteristic of the social behavior of a substantial number of children with ADHD can be described as an apparent lack of a full comprehension of the consequences of their behaviors to others (Nijmeijer et al., 2008). This characteristic resembles the lack of reciprocity that is one of the defining attributes of the social behavior of children with autism spectrum disorders (ASD). The similarities in social difficulties suggest a certain degree of overlap between the two disorders, despite their strict segregation in both the Diagnostic and Statistical Manual of Mental Disorders IV-text revision (DSM-IV-TR; American Psychiatric Organisation, 1994) and the International Statistical Classification of Diseases (ICD-10; World Health Organisation, 1992). This potential overlap is supported by findings of the presence of symptoms of ASD in children with ADHD, and vice versa. The ASD symptoms that are reported to occur most frequently and in a majority of children with ADHD are impairments in social interaction, especially the inability to conceive other individuals' feelings and thoughts (Buitelaar, van der Wees M., Swaab-Barneveld, & van der Gaag, 1999; Clark, Feehan, Tinline, & Vostanis, 1999; Santosh & Mijovic, 2004). Symptoms of communication problems, and stereotyped and repetitive behaviors, have been reported to occur frequently as well in children with ADHD (Clark et al., 1999; Santosh & Mijovic, 2004). A striking finding is that children with ADHD have higher scores on measures of ASD not only in comparison to healthy control children, but also compared to children with psychiatric disorders other than ADHD (Buitelaar et al., 1999; Santosh & Mijovic, 2004). Especially children with the DSM-IV combined subtype have been recently shown to have elevated levels of ASD-symptoms, with nearly one third of boys and three-fourth of girls with combined type ADHD meeting clinical cut-offs for autistic symptomatology (Reiersen, Constantino, Volk, & Todd, 2007).

It has been well established that both ADHD and ASD have a strong genetic background (for reviews see Faraone et al., 2005; Freitag, 2007). Interestingly, two studies in community twin samples have reported that variation in ADHD behaviors partially explain variation in ASD behaviors (Constantino, Hudziak, & Todd, 2003; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). In the most recent of the two, Ronald and colleagues (2008) found genetic influences on autistic and ADHD behaviors in a community twin sample to be overlapping, with ASD and ADHD traits showing a genetic correlation of around 0.50. These studies add to two other findings indicating that ASD and ADHD originate from similar underlying deficits. First, apart

from symptom overlap, overlap in Theory of Mind and executive function deficits between the two disorders has been identified (Buitelaar et al., 1999; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Happé, Booth, Charlton, & Hughes, 2006; Jonsdottir, Bouma, Sergeant, & Scherder, 2006; Nyden, Gillberg, Hjelmquist, & Heiman, 1999; Ozonoff & Jensen, 1999; Yuill & Lyon, 2007). This may point to a shared underlying endophenotype between ADHD and ASD. Second, genetic linkage findings have partially suggested the same genetic regions of interest between the two disorders (Bakker et al., 2003; Ogdie et al., 2003; Smalley et al., 2002; Yamagata et al., 2002).

Interestingly, the three ASD symptom domains have been suggested to originate from distinct genetic influences in both general population samples (Ronald et al., 2006a; Ronald, Happé, & Plomin, 2005; Ronald, Happé, Price, Baron-Cohen, & Plomin, 2006b) and clinical samples (Georgiades et al., 2007; Kolevzon, Smith, Schmeidler, Buxbaum, & Silverman, 2004), although the opposite has been found as well (Dyck, Piek, Hay, Smith, & Hallmayer, 2006; Goin-Kochel, Mazefsky, & Riley, 2008). Thus far, the potential differential heritablility of the ASD dimensions in the context of ADHD has not been investigated.

Furthermore, in studies regarding the overlap between ASD and ADHD, gender has rarely been taken into account. Given the higher prevalence of ASD in boys, one would expect lower levels of ASD in girls with ADHD. This was indeed what was found for autistic symptoms in the international IMAGE sample (Mulligan et al., 2008). However, clinically relevant ASD symptomatology in children with ADHD has also been found to be more prevalent in girls than in boys (Reiersen et al, 2007).
Another understudied topic is how age influences ASD symptoms in children with ADHD. Although social problems are associated with ADHD from early childhood through adolescence and young adulthood (Nijmeijer et al., 2008) this has not yet been investigated for ASD symptoms as such.

In the present study, these issues have been addressed using phenotypic data of Dutch children with ADHD and one of their siblings, which were collected as part of the IMAGE project. Children with autism were excluded from participation, which resulted in a sample where all variation in ASD severity except for the most severe end was represented. Most presently available ASD screening instruments are insufficient for assessing milder, more subtle ASD symptoms, as they are designed to screen for severe forms of ASD. Therefore, in the Dutch IMAGE sample the Children's Social Behavior Questionnaire (Hartman, Luteijn, Serra, & Minderaa, 2006) was used. The CSBQ is particularly suited to measure the continuous distribution of ASD traits in the population as well as in clinical groups other than ASD (Hartman et al., 2006; Luteijn et al., 2000).

The questions we sought to answer in this study are: Firstly, can we confirm previous findings of elevated levels of ASD symptomatology in children with ADHD? Secondly, can we confirm the familiality of ASD symptoms in children with of ADHD?

If so, does subtle ASD symptom familiality depend on ADHD familiality? Thirdly, does this familiality differ for different ASD dimensions? And fourthly, are similar results found for boys and girls with ADHD, respectively, and for younger and elder sibling pairs?

Methods

Subjects

This study reports on data from Dutch participants of IMAGE. IMAGE is a collaborative study in eight European countries (Belgium, Germany, Ireland, Israel, Spain, Switzerland, the Netherlands, and the United Kingdom) that aims to identify genes that increase the risk of ADHD using linkage and association strategies. All probands in IMAGE were aged 5 to 17 at the time of entry into the study, and are of European Caucasian descent. Entry criteria for the probands were a clinical diagnosis of DSM-IV combined subtype of ADHD and having one or more full siblings aged 5-19 available for ascertainment of clinical information and DNA collection. Exclusion criteria applying to both probands and siblings included an IQ < 70, autism (see next section for a detailed description of assessment), epilepsy, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. Whenever possible, families withdrew stimulant medication for one week prior to research assessment to allow for more accurate ascertainment of information on recent ADHD symptom characteristics and severity. For this study, probands with at least one sibling (regardless of his/her ADHD-status) were recruited from families referred to several participating academic child psychiatric outpatient clinics, or from the members of the Dutch Parents' Association. They had undergone clinical evaluations by a pediatrician or child psychiatrist in the recent past. CSBQ data were available for 256 families. For this study, only one sibling was selected at random in case families with two or more participating siblings.

Additional control families were recruited from main stream primary and high-schools from the same geographical regions as the participating families with an ADHD proband. Principals were asked permission to contact the parents of their pupils. Parents who gave permission received questionnaires by mail. Control children had to obtain non-clinical scores (i.e., <63) on both the Conners' parent and the Conners' teacher ADHD/DSM-IV total-subscale. The control sample consisted of sibpairs and singletons, aged 5 to 19. From each pair, one sibling was selected with preference given to boys over girls.

The final sample was formed by 256 DSM-IV ADHD combined type probands (219 boys) and 256 siblings (131 boys), and 147 control children (89 boys). Characteristics of these groups can be found in Table 1.

Diagnostic Instruments

Children already diagnosed with ADHD as well as their siblings were screened using the standard IMAGE procedures as described by Brookes and colleagues (2006). Briefly, screening questionnaires, i.e., the parent and teacher Conners' rating scales, long forms (Conners, 1996), and the parent and teacher Strength and Difficulties Questionnaires (Goodman, 1997), were used to identify children with ADHD-symptoms. T-scores ≥ 63 on any Conners' ADHD/DSM-IV subscale and scores >90th percentile on the parent or teacher SDQ-hyperactivity scale were considered as clinical. Concerning all patients already diagnosed with ADHD and siblings scoring clinically on the parent or teacher Conners' or SDQ, a semi-structured, standardized, investigator-based interview was administered separately for each child; the Parental Account of Childhood Symptoms (PACS; Taylor, 1986). The PACS covers DSM-IV symptoms of ADHD, conduct disorder, oppositional defiant disorder, anxiety, mood, and other internalizing disorders. The most prevalent comorbid disorders in probands as assessed by the PACS were oppositional defiant disorder (152 probands, 59.3%) and anxiety disorder (147 probands, 57.4%). 45 probands (17.6%) had no comorbid disorder.

A standardized algorithm was applied to the PACS to derive each of the 18 DSM-IV ADHD-items, providing operational definitions for each behavioral symptom. These were combined with items that scored 2 or 3 on the ADHD/DSM-IV total-subscale from the Conners' Teacher Rating Scale-Revised: Long Form (Conners' teacher), to generate the total number of items from the DSM-IV symptom checklist. Situational pervasiveness was defined as some symptoms occurring within two or more different situations from the PACS interview, as well as the presence of one or more symptoms scoring 2 or more from the ADHD/DSM-IV total subscale of the teacher rated Conners'.

Children were excluded from participation in IMAGE when classical or atypical autism was diagnosed. This was regarded to be present in case of a clinical score (i.e., ≥ 15) on the SCQ and the presence of ASD symptoms in at least two out of three DSM-IV autism domains, together with a developmental delay in at least one autism domain before the age of 3, as assessed by the section on autistic disorder of the PACS interview. Weight was given especially to symptoms that distinguish ASD from ADHD, and a lack of relationships with peers alone was not sufficient for social impairment of the autistic type. The mean SCQ scores in the final sample were 9.2 (sd 5.6) for probands and 5.4 (sd 4.4) for siblings. No SCQ data were available for controls. Reported SCQ scores in normal controls range from 4.2 (Rutter et al., 1999) to 1.69 (Farzin et al., 2006).

Measures

ASD symptoms

The CSBQ contains 49 items scored on a 3-point Likert-scale. It contains items that refer directly to DSM-IV criteria for autism, but it also represents less severe variations of these criteria as well as ASD associated problems, such as problems in executive functioning and disruptive behavior. Because of this it also captures behavior problems as seen in children with milder variants of ASD. Age and gender specific T-scores were used for all analyses in this paper, and were calculated based on a general population sample of 2,507 Dutch children aged 5 to 17 who have been described in the Dutch CSBQ manual (Hartman, Luteijn, Moorlag, De Bildt, & Minderaa 2007a, 2007b). CSBQ items are grouped in six subscales called "not optimally tuned to the social situation" (tuned; 11 items addressing emotional overreacting and stubbornness/disobedience), "reduced contact and social interest" (social; 12 items), "orientation problems in time, place, or activity" (orientation; 8 items), "difficulties in understanding of social information" (understanding; 7 items), "fear of and resistance to changes" (change; 3 items), and "stereotyped behavior" (stereotyped; 8 items). Estimates for internal, test-retest, and inter-rater reliability, and for convergent and divergent validity were good (Hartman et al., 2006). The CSBQ appears to differentiate between autism and Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS) on the one hand, and PDDNOS and ADHD on the other (Geurts, Luman, & Van Meel, 2008; Hartman et al., 2006). Furthermore, to assess the content validity of the CSBQ, it has previously been compared to an autism screening instrument, the Autism Behavior Checklist (ABC; Krug, 1980). A strong correlation of 0.75 was found between the total scores of both questionnaires in a large Dutch population sample (Luteijn, Minderaa & Jackson, 2007) confirming that what the CSBQ measures correlates strongly with what more stringent autism measures pick up. In the present sample, the Pearson's correlation between the SCQ and CSBQ (raw) total score was 0.52 ($p<0.01$), indicating that these questionnaires assess similar but not identical behaviors.

Two CSBQ subscales, i.e., the tuned and the orientation subscale, tap dysfunctional social behaviors that are conceptually closely related to the ADHD dimensions hyperactivity/impulsivity and attention problems, respectively. These behaviors occur frequently in children with ASD, as is recognized in DSM-IV as well. By including these subscales in the analyses, it will be possible to investigate whether the relation between ADHD and ASD symptoms is carried mainly by these behaviors, or also by more ASD specific behaviors represented in the other subscales.

ADHD-symptoms

The Conners' parent rating scale, long form was applied as a measure of ADHD symptom severity. Items are scored on a four-point Likert scale. Analyses were carried out using T-scores for the DSM-IV symptoms subscales, i.e., the inattentive, the hyper-

active-impulsive and the total scale. The latter is calculated by adding up the inattentive and hyperactive-impulsive subscales. We used the DSM-IV scales because these most closely reflect the current ADHD definition, whereas other scales contain some items that are ADHD-related, but somewhat less ADHD specific. For the 9 siblings who were 18 or 19 at the time of data-collection we applied the 15-17 year age norms.

Anxiety

The anxious-shy scale of the Conners' parent rating scale, long form, was used to assess anxiety, which is a potential confounding factor of the association between ADHD and ASD. T-scores were used for this scale as well, which consists of 6 items scored on a four-point Likert scale.

Intelligence

Full-scale IQ was estimated by four subtests of the Wechsler Intelligence Scale for Children - Third Version (WISC-III) or Wechsler adult intelligence scale-Third version (WAIS-III) depending on the child's age: Vocabulary, Similarities, Block Design, and Picture Completion (Wechsler, 2000; Wechsler, 2002). The subtests are known to correlate between 0.90-0.95 with full-scale IQ (Groth-Marnat, 1997). As the WISC-III is not officially suited for 5-year-olds, data from these children (1 proband and 9 siblings) were excluded from the analyses where IQ was included as a covariate.

Analyses

Group differences in age, IQ, and T-scores on the CSBQ and the Conners' parent DSM-IV symptom subscales between probands, siblings, and controls were assessed with univariate analyses of variance (ANOVAs). Effect sizes η^2 0.01, 0.06 and 0.14 were considered small, medium and large, respectively, following Cohen's standard (1988). To test whether subtle ASD symptoms occur more frequently in children with ADHD and their siblings than in controls, the following contrasts were defined: probands versus siblings, and siblings versus controls. The Kruskal-Wallis test, followed by Mann-Whitney tests, was used to determine differences in gender distribution between probands, siblings and controls.

The relation between ADHD severity and ASD severity was assessed by calculating Pearson's correlations between Conners' parent total scores and CSBQ subscale scores in probands (phenotypic correlations). Correlations were also calculated between the CSBQ subscales and the inattentive and hyperactive-impulsive Conners' parent subscales, respectively, to investigate whether the relation between ADHD and ASD symptoms was driven by either ADHD component.

The familiality of ASD symptoms was estimated by calculating Pearson's correlations between proband and sibling scores (sibling correlations) on the CSBQ

scales. To investigate whether findings were robust, these analyses were repeated after partialling out variance based on differences in IQ between siblings. For these analyses, IQ was included as a covariate in a model in which the subjects' CSBQ subscale score was the dependent variable. The residuals of this analysis were used to calculate sibling correlations.

To further evaluate the familiality of ASD symptoms, we expanded these analyses by adding the Conners' parent DSM-IV-total score to the covariates. Correlations between siblings were calculated for the residuals of this model. From these analyses, there are two possible outcomes. First, if including the covariate does not eliminate or diminish the sibling correlations, then the covariate does not uniquely account for the familiality of the other measure. Second, if including the covariate diminishes the sibling correlation, a common genetic mechanism could be shared by both measures. A similar approach can be found in articles by Szatmari and colleagues (2008) and Raskind and colleagues (2000). These analyses were repeated with the Conners' parent DSM-IV inattentive and hyperactive-impulsive scale instead of the total scale. Furthermore, sibling correlations were calculated for the residuals of a model in which the Conners' parent anxious-shy scale was included as a covariate in addition to IQ and the Conners' parent DSM-IV-total score. This was done to verify whether anxiety confounds the association between ADHD and ASD symptom familiality.

The relation between ADHD and ASD symptom familiality was further tested by calculating cross-sibling cross-trait correlations (cross-correlations). If ADHD and ASD share familial influences, sibling Conners' parent DSM-IV symptom scores should be correlated with proband CSBQ scores.

Sibling correlations were calculated separately for male and female probands, and for younger and elder sibling pairs, respectively. For the latter, a median-split based on proband age was made. Siblings were divided in younger siblings (<11 years) and elder siblings (≥11 years), based on the proband age median. Age concordant pairs (i.e., both siblings and proband either under or above the median split) were formed, with 88 younger and 65 elder sibling pairs. To determine whether sibling pairs with male and female probands, and younger and elder sibling pairs, respectively, showed different correlations, Fisher's z-score transformations and t-tests were calculated using freely available software (Preacher, 2002).

All other analyses were carried out using Statistical Package for the Social Sciences Version 15. We used an alpha of 0.01 to indicate statistical significance for all analyses on the full sample, and an alpha of 0.05 for the analyses of male and female probands and younger and elder sibling pairs, respectively.

Results

Table 1 presents general characteristics and symptom scores of probands, siblings, and controls. ADHD probands had the lowest IQ, followed by their siblings. Controls had the highest IQ. The percentage of males was higher in the proband group than

Table 1 Characteristics for probands, siblings, and controls

	Probands (n=256)	**Siblings (n=256)**	**Controls (n=147)**			
Characteristic	Mean (SD)	Mean (SD)	Mean (SD)	ANCOVA's	η_p^2	Planned contrasts[a]
Age	11.3 (2.6)	10.9 (3.5)	11.2 (3.0)	F(2,650)=1.03		0.36
IQ	98.3 (12.5)	102.0 (11.6)	106.6 (9.9)	F(2,646)=23.04	0.07	<0.001[a]
ADHD-symptom-scores						
Conners' DSM-IV total	76.5 (8.7)	55.3 (12.3)	46.5 (4.4)	F(2,656)=539.82	0.62	<0.001[b]
DSM-IV inattentive	70.7 (8.4)	54.1 (11.8)	46.4 (5.0)	F(2, 656)=367.88	0.53	<0.001[b]
DSM-IV hyperactive-impulsive	78.7 (9.1)	55.6 (12.8)	47.3 (4.8)	F(2, 656)=555.36	0.63	<0.001[b]
ASD-symptoms						
CSBQ-total	72.0 (13.1)	57.5 (12.8)	46.4 (6.2)	F(2,656)=257.05	0.44	<0.001[b]
tuned	92.8 (12.6)	58.1 (12.5)	46.6 (7.4)	F(2,656)=252.77	0.44	<0.001[b]
social	62.1 (15.5)	54.5 (14.3)	47.5 (6.5)	F(2,656)=56.95	0.15	<0.001[b]
orientation	73.4 (15.4)	55.7 (13.3)	46.3 (5.8)	F(2,656)=230.90	0.41	<0.001[b]
understanding	69.4 (13.7)	57.8 (13.4)	48.0 (7.4)	F(2,656)=145.3	0.31	<0.001[b]
stereotyped	68.4 (18.9)	53.1 (13.6)	47.8 (7.7)	F(2, 656)=109.15	0.25	<0.001[b]
change	61.7 (16.1)	52.5 (11.5)	48.8 (9.3)	F(2,656)=54.43	0.14	<0.001[c]
Gender	N (%)	N (%)	N (%)	Kruskal-Wallis		
Boy	219 (85.5)	131 (51.2)	89 (60.5)	H(2)=71.04		<0.001[d]
Girl	37 (14.5)	125 (49.8)	58 (39.5)			

Note: ADHD=Attention-deficit/Hyperactivity Disorder; ANOVA=Analysis of Variance; ASD=Autism Spectrum Disorders; CSBQ=Child Social Behavior Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

[a] probands < siblings < controls (p<0.001); [b] probands > siblings > controls (p<0.001);
[c] probands > siblings > controls (p<0.01); [d] probands > siblings (p<0.001), siblings=controls

in the sibling and control group, which in turn had similar male to female distributions. All T-scores on the CSBQ scales and the Conners' parent DSM-IV-symptoms scales showed significant group differences, with large effect sizes for all scales. Planned contrasts indicated that probands had more subtle ASD and ADHD symptoms than siblings, and that siblings had more ASD and ADHD symptoms than controls.

Phenotypic correlations between the ASD and ADHD symptom scores are presented in Table 2. Correlations between CSBQ subscales and the Conners' parent DSM-IV-symptom scores were all statistically significant, with the exception of that between the CSBQ social and the Conners'parent DSM-IV hyperactive impulsive scale. The CSBQ total score correlated 0.40 ($p<0.001$) with the Conners' parent DSM-IV-total score. As expected, the tuned and the orientation subscales correlated the strongest with the Conners' parent DSM-IV-total score, namely 0.38 ($p<0.001$) and 0.42 ($p<0.001$), respectively. CSBQ subscales that measure core problems of ASD, i.e., social, understanding, stereotyped and change, showed somewhat lower correlations with the Conners' parent DSM-IV total score (between 0.16 and 0.27). These positive correlations confirm the association of ASD with ADHD symptoms. Correlations between the CSBQ and the Conners' parent DSM-IV inattentive and hyperactive-impulsive scales, respectively, showed no apparent differences in strength for all but the social and orientation subscales (see Table 2). These appeared to correlate stronger with the Conners'parent inattentive than with the hyperactive-impulsive subscale (0.23 and 0.46 for the inattentive, and 0.08 and 0.27 for the hyperactive-impulsive scale, respectively).

Table 2 Within proband correlations between ASD symptoms and ADHD symptoms

	CSBQ-total	**tuned**	**social**	**orientation**	**understanding**	**stereotyped**	**change**
Conners' DSM-IV total	*0.40**	0.38*	0.16**	0.42*	0.27*	0.24*	0.26*
DSM-IV inattentive	0.40*	0.32*	0.23*	0.46*	0.25*	0.25*	0.25*
DSM-IV hyperactive-impulsive	0.30*	0.35**	0.08	0.27*	0.21*	0.19*	0.21*

Note: ADHD=Attention-deficit/Hyperactivity Disorder; ASD=Autisme Spectrum Disorders; CSBQ=Children's Social Behavior Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
*$p<0.001$, **$0.001<p<0.01$

Table 3 shows sibling correlations for the CSBQ subscales. Considering the sibling correlations for the T-scores (second column), evidence of familiality was found. All but two of the ASD subscales showed significant correlations, with the CSBQ total symptom scores correlating 0.28 ($p<0.001$). The CSBQ subscale that showed the strongest sibling correlation was the stereotyped subscale, $r= 0.35$, $p<0.001$.

Table 3 Sibling correlations for proband and sibling ASD symptoms

	A (n=256)	**B (n=246)**	**C (n=246)**	**D (n=246)**	**E (n=246)**	**F (n=246)**
CSBQ-total	*0.28**	*0.27**	*0.30**	*0.29**	*0.25**	*0.27**
tuned	0.16*	0.15	0.12	0.13	0.08	0.08
social	0.18*	0.13	0.12	0.13	0.11	0.1
orientation	0.19*	0.17	0.26*	0.25*	0.19**	0.24*
understanding	0.15	0.15	0.13	0.1	0.14	0.13
stereotyped	0.35*	0.36*	0.37*	0.35*	0.35*	0.36*
change	0.09	0.11	0.09	0.1	0.08	0.09

Note: ASD=Autism Spectrum Disorders; CSBQ=Children's Social Behavior Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
A=Correlations for CSBQ T-scores; B=correlations for CSBQ T-score residuals, i.e., variance remaining after inclusion of IQ as covariate; C=correlations as under B, but with Conners' DSM-IV total score added to covariates; D=correlation as under C, but with Conners' DSM-IV *inattention* score instead of total score; E=correlation as under C, but with Conners' DSM-IV *hyperactive-impulsive* score instead of total score; F=correlation as under C, but with Conners' anxious-shy score added to covariates
*$p<0.001$, **$0.001<p<0.01$

Subsequently, sibling correlations for the CSBQ subscale scores were calculated correcting for IQ. Results can be found in the third column of Table 3. Inclusion of IQ in the analyses did not appear to change the strength of the cross-correlations. Furthermore, cross-correlations of the CSBQ total score, and the subscales orientation and stereotyped remained significant after correcting for the Conners' parent DSM-IV-total score. See Table 3, fourth column for the exact strength of the correlations. The results of the familiality analyses were similar when the Conners'parent inattentive or hyperactive-impulsive subscale were used instead of the total scale (see Table 3, fifth and sixth columns). Anxious-shy behavior did not appear to be a confounding factor in the familiality of ASD symptoms in children with ADHD, as can be seen in the last column of Table 3.

The independence of the ADHD and ASD symptom familiality was also suggested by the cross-correlations between proband ASD symptoms and sibling ADHD scores, which were all very weak and non-significant (see Table 4).

Table 4 Cross-correlations between proband ASD symptoms and sibling ADHD symptoms

	Proband (n=256)						
	CSBQ-total	tuned	social	orientation	understanding	stereotyped	change
Sibling (n=256)							
Conners' DSM-IV total	0.06	0.10	0.06	0.01	0.04	0.02	0.03
DSM-IV inattentive	0.06	0.08	0.03	0.03	0.06	0.01	0.02
DSM-IV hyperactive-impulsive	0.06	0.09	0.07	-0.01	0.01	0.04	0.03

Note: ADHD=Attention-deficit/Hyperactivity Disorder; ASD=Autism Spectrum Disorders; CSBQ=Children's Social Behavior Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

In Table 5 characteristics of the probands used for the subgroup analyses based on gender and age can be found. Female probands showed significantly higher T-scores than male probands for almost all ADHD and ASD subscales. The exception was the CSBQ tuned subscale, which did not differ significantly between boys and girls. Small effect sizes were found for all differences in CSBQ subscale scores. A large effect size was found for the Conners' DSM-IV total scale, and a medium effect size for the hyperactive-impulsive scale. Differences between scores of probands of younger and elder sibling pairs were significant for the CSBQ tuned, social and orientation subscale (small effect sizes), and the Conners' DSM-IV hyperactive-impulsive scale (medium effect size), with younger probands scoring higher on the first two scales, and elder on the latter two.

When sibling correlations were calculated for male and female probands separately, male probands generally showed weaker sibling correlations than female probands (Table 6, columns 2 and 3). For the tuned scale, gender-differences between the correlations for the T-scores, the Conners' parent DSM-IV total corrected residuals, and the residuals corrected for the Conners' parent anxious-shy scale reached statistical significance ($z=2.21$, $p=0.03$; $z=2.51$, $p=0.01$, and $z=2.40$, $p=0.02$, respectively), with female probands showing stronger sibling correlations than male probands.

Table 5 Characteristics for proband subgroups

Characteristic	**Boys (n=219)**	**Girls (n=37)**				**Younger probands (n=88)**	**Elder probands (n=65)**			
	Mean (sd)	Mean (sd)	ANOVAs	η_p^2	p	Mean (sd)	Mean (sd)	ANOVA's	η_p^2	p
Age	11.3 (2.7)	10.8 (2.6)	n.s.			9.0 (1.3)	13.8 (1.9)	n.s.		
IQ	98.3 (12.5)	98.7 (12.8)	n.s.			98.9 (13.4)	97.1 (11.3)	n.s.		
ADHD-symptom-scores										
Conners' DSM-IV total	75.1 (8.2)	84.5 (7.1)	F(1,254)=48.9	0.14	<0.001	76.1 (8.3)	79.0 (9.3)	n.s.		
DSM-IV inattentive	69.3 (7.6)	78.9 (8.0)	F(1,254)=49.1	0.16	<0.001	71.8 (8.7)	71.2 (8.3)	n.s.		
DSM-IV hyperactive-impulsive	77.8 (9.0)	84.5 (7.9)	F(1,254)=18.1	0.07	<0.001	77.3 (8.7)	81.7 (9.0)	F(1,151)=10.0	0.06	<0.01
ASD-symptoms										
CSBQ-total	71.9 (12.3)	79.7 (15.8)	F(1,254)=11.7	0.04	<0.001	73.3 (12.7)	74.6 (14.4)	n.s.		
tuned	72.6 (12.4)	73.9 (14.2)	n.s.			71.3 (11.3)	75.9 (15.3)	F(1,151)=4.5	0.03	<0.05
social	61.1 (14.6)	68.0 (19.0)	F(1,254)=6.33	0.02	<0.05	64.6 (15.8)	58.9 (13.0)	F(1,151)=5.7	0.04	<0.05
orientation	71.9 (14.9)	81.9 (16.0)	F(1,254)=14.0	0.05	<0.001	72.4 (12.5)	77.5 (18.5)	F(1,151)=3.9	0.03	<0.05
understanding	68.2 (13.2)	76.0 (14.5)	F(1,254)=10.6	0.04	<0.01	71.8 (12.8)	68.4 (15.9)	n.s.		
stereotyped	67.1 (17.7)	75.9 (23.7)	F(1,254)=7.0	0.03	<0.01	66.5 (17.7)	62.3 (20.0)	n.s.		
change	60.4 (15.1)	69.4 (19.5)	F(1,254)=10.4	0.04	<0.01	62.1 (14.8)	64.4 (17.4)	n.s.		
Gender						N (%)	N (%)	X^2-test		
Boy						71 (80.9)	58 (89.2)	n.s.		
Girl						17 (19.1)	7 (10.8)			

Note: ADHD=Attention-deficit/Hyperactivity Disorder; ANOVA=Analysis of Variance; ASD=Autism Spectrum Disorders; CSBQ=Children's Social Behavior Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; n.s.=not significant

Table 6 Sibling correlations for subgroups

	Male probands (n=219)	Female probands (n=37)	Younger sibpairs (n=88)	Elder sibling pairs (n=65)
Correlations for CSBQ, T-scores				
CSBQ-total	0.23**	0.44**	0.35**	0.33**
tuned	0.09	0.46**	0.28**	0.26*
social	0.13	0.33*	0.03	0.38**
orientation	0.15	0.24	0.18	0.31*
understanding	0.13	0.24	0.13	0.12
stereotyped	0.33**	0.48**	0.32**	0.37**
change	0.03	0.31	0.21	-0.04
Correlations for CSBQ T-score residuals (variance remaining after inclusion IQ as covariate)				
CSBQ-total	0.24**	0.35*	0.37**	0.37*
tuned	0.09	0.39*	0.29**	0.25
social	0.07	0.24	0.03	0.39**
orientation	0.16*	0.09	0.23*	0.33*
understanding	0.15*	0.09	0.18	0.17
stereotyped	0.31**	0.52**	0.43**	0.39**
change	0.05	0.29	0.22*	0.06
Correlations for CSBQ T-score residuals, Conners' DSM-IV total score added to covariates				
CSBQ-total	0.25**	0.53**	0.40**	0.20
tuned	0.06	0.48**	0.26*	0.05
social	0.08	0.22	0.03	0.30*
orientation	0.24**	0.36*	0.27*	0.26
understanding	0.12	0.24	0.12	0.07
stereotyped	0.30**	0.60**	0.42**	0.33*
change	0.05	0.25	0.23*	-0.07
Correlations for residuals, Conners' anxious-shy score added to covariates				
CSBQ-total	0.22**	0.46**	0.31**	0.21
tuned	0.03	0.44*	0.17	0.03
social	0.07	0.15	-0.04	0.29*
orientation	0.23**	0.31	0.24*	0.26
understanding	0.11	0.28	0.07	0.11
stereotyped	030**	0.55**	0.38**	0.32*
change	0.08	0.13	0.15	0.06

Note: CSBQ=Children's Social Behavior Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

**sibling correlation p<0.01, *sibling correlation p<0.05

Results for the age-matched sibling pairs can be found in the right two columns of Table 6. Younger sibling pairs showed weaker correlations on the social scale than did elder pairs, with significant differences for the T-scores and the IQ corrected data ($z=-2.21$, $p=0.03$ and $z=-2.29$, $p=0.02$, respectively). Differences in sibling correlations between younger and elder pairs for the other subscales were not significant. For elder sibling papers, correlations appeared to decrease in strength when the Conners' DSM-IV total score was included as a covariate, especially for the tuned scale. This suggests that the relation between the familiality of ADHD and ASD symptoms may be age dependent, with possibly more shared familiality between ADHD and ASD symptoms for elder sibling pairs.

Discussion

The current study confirms the high levels of ASD symptoms in children with ADHD (Clark et al., 1999; Luteijn et al., 2000; Reiersen et al., 2007; Santosh & Mijovic, 2004). Our study sample consisted of children with ADHD combined type, a subtype that has previously been reported to have the highest levels of ASD symptoms compared to other ADHD subtypes (Reiersen et al., 2007). Indeed, subtle ASD traits covered by the CSBQ were elevated in the children with ADHD compared to their siblings, with sibling scores still well above those of healthy control children. The elevations in ASD symptoms were not restricted to a specific subset or subscale of ASD symptoms, but covered the whole ASD spectrum, again in line with previous findings (Clark et al., 1999; Reiersen et al., 2007; Santosh & Mijovic, 2004).

A positive relation was found between ADHD and ASD symptoms. This endorses the association between ADHD and ASD. However, ADHD-ASD correlations were of modest strength, indicating that ASD symptoms as measured in this study should not be considered a mere proxy for ADHD severity, but point to a different set of problems. As expected beforehand, correlations were the weakest for the most typical ASD subscales, but even the subscales that are conceptually related to ADHD correlated only moderately with the Conners'scores. For most CSBQ subscales, there was no indication that either symptoms of attention deficit or of hyperactivity-impulsivity alone could explain the association. The most outspoken exception was found for the CSBQ social subscale, which showed a weak and non-significant correlation with hyperactive-impulsive symptoms in contrast to symptoms of attention deficits. This suggests that children with combined type ADHD who have mainly inattention problems may show more withdrawn behavior than primarily hyperactive-impulsive children.

Our findings furthermore suggest that ASD symptoms in the context of ADHD are familial, and that this familiality is largely independent from that of ADHD. This finding

is strengthened by the fact that IQ and comorbid anxiety were found to be unlikely factors confounding the familiality of ASD symptoms. These results speak against substantial common genetic factors for ADHD and ASD. This finding is somewhat surprising given that two studies that have previously addressed the familiality of ASD symptoms point to a shared etiology between ADHD and ASD (Constantino, Hudziak, & Todd, 2003; Ronald et al., 2008). It should be noted, however, that both studies involved general population twin samples rather than clinical samples. Interestingly, in a previous study involving the IMAGE sample, but measuring more stringent autism symptoms, the familiality of ASD and ADHD also appeared to be largely independent, as indicated by rather weak ASD-ADHD correlations between siblings (Mulligan et al., 2008). Our IMAGE findings clearly need independent replication, however.

Our sibling-pair design allows us to only report on familiality rather than heritability. However, previous twin studies suggest ASD is highly heritable (Muhle, Trentacoste, & Rapin, 2004) and that genetic effects rather than shared environmental factors are largely responsible for sibling similarity in ASD symptomatology. Thus, familiality estimates as identified in the present study are likely to be mostly resulting from genetic factors.

It has been reported that different ASD dimensions may be genetically independent (Georgiades et al., 2007; Kolevzon et al., 2004; Ronald et al., 2005; Ronald et al., 2006a; Ronald et al., 2006b). In line with this, we found different sibling correlations for the different CSBQ subscales. The CSBQ subscale 'stereotyped behavior' appeared to show the strongest correspondence between siblings. It contains items referring to repetitive movements and sensory stereotypies. The potential dissimilarity in heritability of different ASD dimensions in children with ADHD is a new finding, and needs to be considered in future research.

In line with the study by Reiersen and colleagues (2007), we found elevated levels of subtle ASD symptoms in both boys and girls with ADHD. In fact, girls with ADHD had even higher gender and age specific CSBQ scores than boys, also similar to what Reiersen and colleagues (2007) found. Therefore, despite the fact that boys are over-represented in ASD in general, in children affected with combined type ADHD girls are at least as affected with ASD symptoms as are boys. Furthermore, our results suggest that ASD symptoms are more familial when girls are affected, although this needs to be confirmed in a twin sample. This is inconsistent with previous studies indicating that the familial loading is similar in families of boys and girls with ASD, and that that the genes that influence autistic traits are the same for both genders (Constantino & Todd, 2003; Goin-Kochel, Abbacchi, & Constantino, 2007). It should be noted, however, that these studies pertain to ASD while our study focused on subtle ASD symptoms within ADHD.

We observed some differences in familiality for subtle ASD traits in younger versus elder sibling pairs, especially with regard to the social subscale. As far as we know, no

data have been published about heritability changes depending on age for ASD symptoms. Nevertheless, it has been found that prosocial behavior shows declining shared environmental and increasing genetic influences with increasing age (Knafo & Plomin, 2006; Scourfield, John, Martin, & McGuffin, 2004). This corresponds with our findings of higher familiality of the social scale, which is negatively correlated with prosocial behavior, in elder sibling pairs.

One of the limitations of this study is that it involved clinically referred children with combined type ADHD. Our findings in this highly selected sample therefore cannot be translated directly to ADHD in the general population. Furthermore, despite a diagnosis of autism being one of the exclusion criteria of the IMAGE study, a few children with comorbid ASD may still have been included in our sample. We think that as such our sample is representative of current clinical practice, where sometimes ASD may go unnoticed when ADHD symptoms dominate the clinical picture. Another issue is that, perhaps besides a rare exception, the majority of children in our sample had ASD traits below the autism cut-off. We do not know whether the underlying genetic factors for these subtle ASD features are the same for full blown autistic symptoms. However, findings from a study using the social responsiveness scale, an instrument similar to the CSBQ, do suggest so (Constantino et al., 2006). Although representative of clinically relevant ADHD, our sample was predominantly male. We found interesting gender differences with regard to the familiality of ASD symptoms, but these findings need replication in samples with more females represented. Also, the cross-sectional nature of our study limits the interpretation of the age effects, which clearly deserve further study in a longitudinal design. Finally, we used parent reports only whereas, ideally, a detailed developmental history and observational data should be collected to assess autistic symptomatology.

In conclusion, this study demonstrates that both boys and girls with combined type ADHD have increased levels of ASD symptoms. Although the major classification systems (DSM-IV and ICD-10) discourage diagnosing a combination of ADHD and ASD, our results as well as others' speak against this strict segregation. Furthermore, we found the familiality of ASD symptoms to be largely independent of the familiality of ADHD. Of all ASD dimensions, stereotyped behavior showed the strongest familiality. Our results suggest that ASD familiality may be higher in ADHD affected girls than in boys, but our female sample was of limited size. ASD familiality appeared age dependent, which stresses the importance of taking age into account when interpreting genetic study results and comparing between such studies. Future research may try to elucidate the genetic loci involved in ASD symptoms in the context of ADHD in comparisons with genetic findings in ASD as such. The implications of the presence of ASD symptoms for the prognosis and treatment of children with ADHD need attention.

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